Reply to 'Letter to Editor by Finsterer J and Zarrouk-Mahjoub S : Phenotypic manifestations of the m.8969G > A variant'

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LETTER TO EDITOR

Reply to 'Letter to Editor by Finsterer J and Zarrouk-Mahjoub S: Phenotypic manifestations of the m.8969G>A variant'

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Sir,

We thank Drs Finsterer and Zarrouk-Mahjoub for their interest in our recent paper describing a family with two siblings affected by a mitochondrial disorder caused by a rare mitochondrial DNA variant m.8969G>A [1]. Their letter provides us with the opportunity to make specific points clearer.

The authors wonder why our patients' spectroscopy was normal while CSF was elevated, and pay attention to this discrepancy. We agree that it is puzzling when cerebrospinal fluid (CSF) lactate was increased whereas spectroscopy (^{1}H-MRS) did not show a lactate peak although they were taken on the same day. Spectroscopy is a sensitive tool in diagnosis of brain lactate, if the site of interrogation is correct, which may be difficult when brain MRI is normal [2, 3]. Mitochondrial disease usually affects only specific regions of the brain, and in our case with normal MRI, the spectroscopy was investigated from the thalamus. Multi-region spectroscopy might have better detected the affected area in the brain [4].

Additionally, they ask for more detailed clinical data of the patients and their family members, which we are happy to provide.

No family members of these siblings had clinical signs of a mitochondrial disorder: parents and the other two siblings were healthy, the maternal grandmother had had migraine, but was otherwise healthy, as was her sister. No family members underwent histological or biochemical examinations. The threshold for manifesting disease is unknown for this particular variant, but healthy members in our family had much lower heteroplasmy levels in blood (< 1–18%) than the asymptomatic mother (49%) described by Wen et al. [5]. Unfortunately, we had no opportunity to determine heteroplasmy of other tissues than described in the table, but heteroplasmy has been at a high level in all affected patients in all tissues studied (blood 61–96%, fibroblasts 85–96%, muscle 88–95%, kidney 89% and urine 79%) [1].

None of the family had seizures. The affected brother had asymptomatic centrotemporal spikes during sleep, while otherwise normal EEG. Both affected siblings had been examined and followed up by an ophthalmologist. They had no optic atrophy nor findings typical for Leber's hereditary optic neuropathy, only mild tortuosity of the retinal vessels without clinical symptoms. Visually evoked potentials had not been examined. No medication had been used, but rehabilitation therapies and dietary measures were ongoing.

Lastly, we would like to comment that Finsterer and Zurrocuk-Mahjoub calculated a modified Yarham score, the score which was established specifically for MT-tRNA mutations [6], to the MT-ATP6 m.8969G>A variant to be 11, indicating the variant as 'probably pathogenic'. We consider that the following facts support the pathogenic role of this variant: more than one previous independent reports, the base is evolutionarily conserved, the variant is heteroplasmic, the variant segregates with the disease in the pedigree, and ATP production was decreased in our patient. Furthermore, studies in yeast [5] confirm the pathogenicity of this variant.

We hope that with these additions and clarifications, our report would benefit both to clinicians and scientist in the fascinating field of mitochondrial diseases.

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